IDENTIFYING THE COMMON BARRIERS OF PATIENT RECRUITMENT AND RETENTION OF WOMEN IN HIV/AIDS CLINICAL TRIALS TO DETERMINE THE BEST PRACTICES IN MINIMIZING UNDER-ENROLLMENT AND WITHDRAWS FROM CLINICAL STUDIES

By
Katie Ta

A thesis submitted to Johns Hopkins University in conformity with the requirements for

the degree of Master of Science

Baltimore, Maryland

May 2020

Abstract

Purpose: Many past human immunodeficiency virus (HIV) clinical trials have struggled to recruit and retain female participants due to their encounters with potential barriers that prevented the participants' initial or continued involvement in the clinical trials. Patient recruitment and retention rates are crucial to the success of clinical research trials. The objective of this study was to identify common barriers to recruitment and retention of female participants and to identify the common best practices used to address these barriers.

Methods A literature search was conducted to identify articles relating to the recruitment and retention of female participants in HIV/AIDS clinical trials. Keywords and search terms were used in PubMed, BASE (Bielefeld Academic Search Engine), and Web of Science. A total of 48 articles were found and narrowed down using 17 out of the 27 checklist items provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to help determine each article's eligibility for inclusion in this study.

Results: In the twenty-five articles selected for this study, eight common recruitment and retention barriers were identified. Researchers addressed these barriers by utilizing several common best practices to improve recruitment and retention rates.

Conclusion: By implementing the best practices found in this study, healthcare providers and researchers will be able to overcome the challenges in recruiting and retaining female participants in future HIV/AIDS clinical trials.

Primary Reader and Advisor: Dr. Jeffrey Kantor

Secondary Reader: Justin Lew

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

According to the National Institute of Health, clinical studies involve research using voluntary human subjects or participants. The purpose of these studies is to help contribute medical knowledge to the healthcare and research communities. There are two main types of clinical studies: observational studies and clinical trials (interventional studies).[1]

In clinical trials, the participants receive specific interventions according to the research plan created by the principal investigator, often a medical doctor. Interventions may include, but are not limited to, pharmaceutical products, drugs, devices, procedures, and diet.

Clinical studies are conducted to advance medical knowledge related to treatment, diagnosis, prevention of disease. Clinical studies can also help doctors determine other aspects of care, such as improving the quality of life for people with chronic illnesses such as HIV.[2] The goal of clinical trials is to determine if a new test or treatment is safe and if it works.

1.1 Importance of Participating in Clinical Trials

[1] Learn About Clinical Studies. (n.d.). Retrieved from https://clinicaltrials.gov/ct2/about-studies/learn#WhatIs
[2] Why Should I Participate in a Clinical Trial? (2019, May 30). Retrieved from https://www.nih.gov/health-information/nih-clinical-research-trials-you/why-should-i-participate-clinical-trial

A clinical study is conducted based on a research plan or protocol. Protocols are intended to answer specific research questions and to protect participants. Protocol information may include, but is not limited to:

- Reasons for conducting a study,
- Eligibility criteria (a predetermined group of people based on gender, race, age, disease, etc.)
- Number of participants needed
- Schedule of procedures and tests
- Type of drugs administered
- Length of study

Factors that could lead to poor results in clinical trials may include the following: length of the clinical study, costs, and time burdens on patients. Issues can arise during clinical trials that may result in clinical failures, including safety issues, lack of efficacy, lack of funding, and lack of patient recruitment or retention.[3]

An article by Hwang et al. [4] assessed 640 phase 3 trials; the authors found that 54% failed in clinical development and 57% failed due to inadequate efficacy. Many reasons could contribute to failed efficacy, such as non-response to treatment drugs, flawed study design, small sample size due to patient dropouts, and insufficient enrollment, causing an

[3] Fogel D. B. (2018). Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemporary clinical trials communications*, *11*, 156–164. https://doi.org/10.1016/j.conctc.2018.08.001

[4] Hwang T.J., Carpenter D., Lauffenburger J.C., Wang B., Franklin J.M., Kesselheim A.S. Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA Intern. Med. 2016;176:1826–1833

inappropriate statistical endpoint. Regardless of the type of research, clinical trials are heavily dependent on the participation of patients to conduct a research study successfully.

The purpose of a clinical trial is to answer a research question; for this to happen, researchers must recruit an adequate number of participants to conduct the clinical study and must retain as many of those participants as possible. In clinical trials where either recruitment or retention falls short, the study may fail to achieve its purpose. Researchers will be unable to answer the research question, and the enrolled participants would have joined the clinical research study for no purpose. Recruitment and retention of participants are essential in the success of clinical studies, but maintaining high recruitment and retention rates in clinical trials is a significant challenge across the research community.

Chapter 2

Review of the Literature

2.1 History of HIV Clinical Trials

According to the National Institute of Allergy and Infectious Disease (NIAID), in 1984, Human Immunodeficiency Virus (HIV) was identified as the cause of Acquired Immunodeficiency Syndrome (AIDS). Historically, vaccination has been the preferred method for protecting people from infectious diseases. In 1987, the first HIV vaccine clinical trial opened at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. The Phase 1 trial enrolled 138 healthy, HIV-negative volunteers. The vaccine showed no serious adverse effects. Although some other methods and techniques do help prevent HIV infection, nevertheless, vaccination has always played a vital role in ending the HIV pandemic. There are

two approaches to HIV vaccine development: 1. A Theoretical Approach; 2. An Empirical Approach.[5] This thesis will mainly focus on an empirical approach.

A Theoretical Approach is based on theory and involves establishing an understanding of the immune response to HIV infection and finding ways to generate and enhance that response through vaccination. Some strategies aim to prevent HIV infection through an antibody-mediated response, while others strive to create a protective cellular response.[6]

An Empirical Approach to HIV vaccine development relies on observation and experimentation to move vaccine candidates into clinical trials. The sole purpose of a vaccine trial is to contribute towards scientific and medical progress. Many investigational vaccines that initially worked in laboratory and animal studies did not do well in human clinical trials. An example of this was in 2007, where two large HIV vaccine clinical trials, known as the *STEP* and *Phambili,* were run. The administration of vaccinations ended without success. After reviewing the data put out by an independent data safety and monitoring board, it was concluded that the data did not demonstrate that the vaccine could either prevent HIV infection or affect the course of the disease in people who acquired HIV; however, in 2003, the Thai HIV RV144 study in Thailand was the first large clinical trial to demonstrate the effectiveness of an investigational HIV vaccine. "At the end of the 3.5-year study period, investigators observed a 31 percent reduction in HIV infection among vaccine recipients compared to those who received a placebo.

[5] History of HIV Vaccine Research. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history

[6] A Theoretical Approach To HIV Vaccine Development. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/theoretical-approach

The trial, which involved more than 16,000 adult participants, was sponsored by the US Military HIV Research Program, in collaboration with NIAID and other partners".[7]

The RV144 study evaluated the safety and effectiveness of a prime-boost combination of two vaccine components given in sequence: ALVAC-HIV and AIDSVAX B/E. The vaccine regimen appeared to provide the most significant protective effect during the first year after vaccination, providing a 60 percent reduction in infection risk, but over time the effectiveness decreased. The results from the study indicated the vaccines were safe, well-tolerated, and suitable for a larger scale research clinical research.[8] The NIAID and its partners continue to invest in multiple approaches to develop an effective HIV vaccine.

2.2 History of Clinical Trials Involving Women

In the past several decades, there has been a significant shift in scientific, ethical, and legal standpoints regarding the inclusion of women in clinical trials conducted in the United States. There is a clinical requirement for testing drugs in specific populations, such as women, to ensure correct dose regimens and to minimize the adverse effects of the treatment. The women's movement between the 1960s and 1970s began to take effect in the 1980s when the US Public Health Service established a task force on women's health. The task force concluded that a lack of research in women's health had compromised the quality of available information

[7] An Empirical Approach to HIV Vaccine Development. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/empirical-approach

[8] An Empirical Approach to HIV Vaccine Development. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/empirical-approach

on diseases affecting women and the health care women receive. The task force recommended that steps be taken to ensure that more women's participation was included in clinical trials.[9]

The 1977 Food and Drug Administration (FDA) guidelines had excluded women of childbearing potential from the first and the earliest part of the second phase of clinical trials. Sponsors often interpreted the restriction more generally and limited entry of women into the later stages of drug trials. The FDA recognized that failure to include diverse populations in trials for new drugs could lead to treatment protocols focused more on middle-aged, white males. In a 1983 survey of 11 pending new drug applications, the agency found substantial enrollment disparities, with women and the elderly significantly underrepresented in some disease study categories.[10] In response, the NIH issued a policy in 1986 to encourage the inclusion of women in federally funded research studies; however, the US General Accounting Office (GAO) found that the NIH had made little progress concerning implementing its policy. This failure led to the enactment of The Women's Health Equity Act of 1990. After the passing of the Act, NIH created an Office for Research on Women's Health to ensure that women's health research is an integral part of the scientific fabric at NIH and throughout the scientific community.[11]

Many factors can influence drug responses in people such as age, gender, race, and pre-existing diseases. Any of these can influence healthcare providers' choices of medications for their patients. For women, hormonal variations associated with the menstrual cycle,

[9] Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal Issues Merkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 – 84
[10] Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal Issues Merkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 - 84
[11] Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal Issues Merkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 - 84

menopause, oral contraceptive use, or estrogen supplementation may cause the drug to have a different effect on participants; therefore, the value of individualized treatment for a specific population became essential and drove the need to include women in clinical trials for AIDS therapy.

According to the AIDS Service Center of the HIV Law Project, in January 1992, only 1,151 women had been included among the 14,799 participants enrolled in the AIDS Clinical Trials Group studies sponsored by the NIAID.[12] To ensure that new drugs would be evaluated adequately in women, in 1993, the FDA issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. According to the guidelines, researchers were to include a "reasonable" number of women in new clinical trials. The instructions also highlighted the need to assess possible pharmacokinetic differences (drug concentrations in the blood and tissues based on gender) and conduct pharmacodynamics (effect of drugs on the body) studies to evaluate the body's response to a given level of a drug when efficacy, rates of adverse events, and dose-response differed by gender.

Examination of drugs relative to women's natural hormonal background was required, as were drug interaction studies with hormonal contraceptive agents, and hormone replacement therapy. At the same time, the guideline influenced the agency's decision to reverse the 1977 policy that had effectively barred most women of childbearing potential from participating in the early stages of clinical trials.[13] The new requirements for the inclusion of

[12] Pearl et al., 1992Pearl, M., Banzhaf, M., Leger, A., and Long, I.L. Women in U.S. government clinical trials. Amsterdam, Netherlands; 1992 (VIII International Conference on AIDS, 8(2:B235))

[13] Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal Issues Merkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 - 84

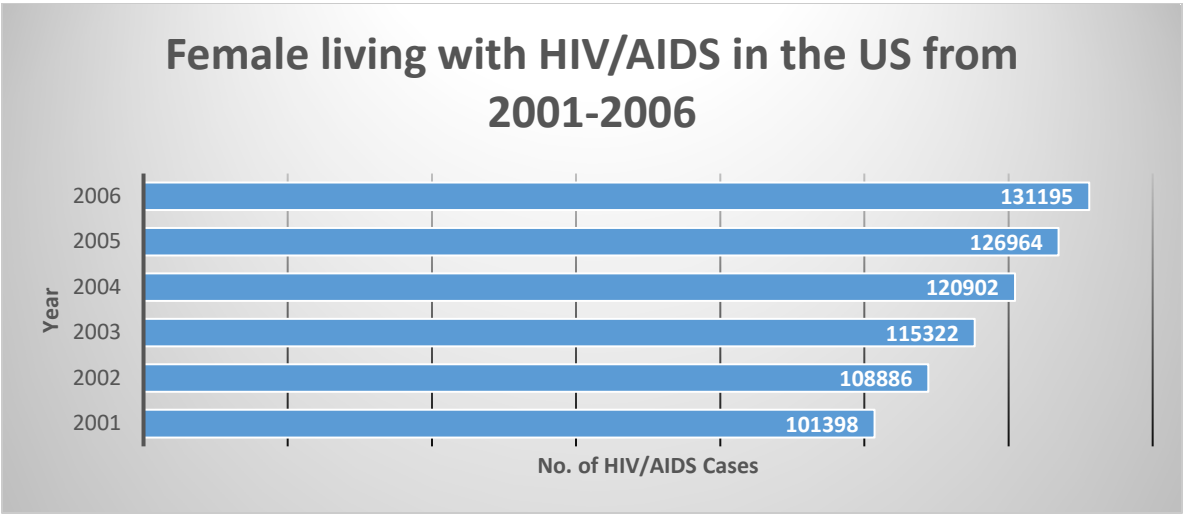
women in federally funded clinical trials also were integrated into the NIH Revitalization Act of 1993. One year later, a new NIH guideline was jointly issued by the Office of Research on Women's Health to ensure that women and their subpopulations were included in all human subject research. Importantly, these groups must be able to participate in Phase 3 clinical trials to allow an accurate analysis of differences in intervention effects. Grant proposals being considered by any institute within the NIH had to be reviewed for compliance with this guideline, and funding may have been denied if guidelines were not met.[14] Although progress has been made, women still appear to be underrepresented in some important clinical trials, particularly in the area of HIV and AIDS.[15,16]

According to the 2006 CDC HIV/AIDS Surveillance Report of the estimated 491,727, HIV/AIDS cases in US 27% (132,766) were female. Figure 1 illustrates the number of women living with HIV/AIDS per year between the years of 2001 to 2006. Female HIV/AIDS has increased steadily from 101,398 cases in 2001 to 131,195 cases in 2006, a 23% increase. With an average of 117,444 HIV/AIDS cases throughout six years.

[14] Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal Issues Merkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 – 84

[15] Institute of Medicine (US) Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies; Mastroianni AC, Faden R, Federman D, editors. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies: Volume I. Washington (DC): National Academies Press (US); 1994. 2, Women's Participation in Clinical Studies. Available from: https://www.ncbi.nlm.nih.gov/books/NBK236535/

[16] Metch, B., Frank, I., Novak, R., Swann, E., Metzger, D., Morgan, C., . . . Koblin, B. (2013). Recruitment of urban US women at risk for HIV infection and willingness to participate in future HIV vaccine trials. AIDS Behav, 17(2), 760-772. doi:10.1007/s10461



2.2 Figure 1: Female living with HIV/AIDS in the US from 2001-2006 data retrieved from https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2005-vol-17.pdf

As female HIV/AIDS cases increase steadily in the US, there is a need to reduce the number of challenges/barriers that affect the amount of women participation in HIV/AIDS clinical research. There is a limited amount of information available for HIV/AIDS clinical trials that involve women.

In 2014 twenty three percent of all United States HIV cases were women. Most data available to the public regarding the effectiveness and safety of HIV drugs were based on research studies done on men.[17] With a limited number of clinical research studies done on women living with HIV/AIDS, there is not an adequate amount of information regarding the effectiveness and safety of HIV drugs that were administered to women. Although there was an increase in clinical studies done on HIV prevention and treatment, women's participation remained low.

[17] 20, S. on M. (2019, August 29). Lessons from GRACE: A US Study Focused on Women Living with HIV. Retrieved from https://www.thewellproject.org/hiv-information/lessons-grace-us-study-focused-women-living-hiv.

2.3 Issues of Recruitment and Retention

In recruitment and retention of a diverse population in antiretroviral (ARV) clinical research. Approximately twenty-five percent of new HIV diagnoses in the United States were women. Although there has been an increase in clinical trials, women remain underrepresented in clinical trials of ARV agents for HIV.[18] Although there has been an increase in clinical trials, women remain underrepresented in clinical trials of ARV agents for HIV.[19] As a result, current treatment guidelines are based on data from clinical trials that primarily enrolled men. Although the number of women recruited into clinical trials has been increasing, recruitment and retention of 'treatment-experienced' (An HIV patient that has previously or is currently taking antiretroviral drugs) women in trials have been less successful.[20]

Several barriers prevented the successful recruitment and retention of women in clinical trials. In 2005, the Cargill and Stone article found that women who occupy primary care roles in their families placed family commitments above their own medical needs. Additional factors that impacted regular access to healthcare and led to missed medical appointments included domestic violence/threats of violence, the use of illicit drugs, and perceived stigma about their HIV status.[21] Innovative approaches to trial design and conduct are required to overcome the

[18] Centers for Disease Control and Prevention. HIV/AIDS among women. www.cdc.gov/hiv/topics/women/resources /factsheets/pdf. [Jul 20;2010] www.cdc.gov/topics/women/resources/factsheets/pdf.

[19] Falcon, R., Bridge, D. A., Currier, J., Squires, K., Hagins, D., Schaible, D., . . . Mrus, J. (2011). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. *J Womens Health (Larchmt), 20*(7), 1043-1050. doi:10.1089/jwh.2010.2504

[20] Falcon, R., Bridge, D. A., Currier, J., Squires, K., Hagins, D., Schaible, D., . . . Mrus, J. (2011). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. *J Womens Health (Larchmt), 20*(7), 1043-1050. doi:10.1089/jwh.2010.2504

[21] Cargill, V. A., & Stone, V. E. (2005). HIV/AIDS: a minority health issue. *Med Clin North Am, 89*(4), 895-912 doi:10.1016/j.mcna.2005.03.005

barriers and achieve successful participation in clinical trials. The scientific evidence and clinical experience suggest that there may be multiple factors limiting the recruitment and retention of female subjects. For example, a young woman with a family may be hesitant to enroll in a study that presents potential risks to her safety, livelihood, and children. A working mother may also be reluctant to participate because she may be unable to incorporate the behavioral requirements of the study into her daily schedule.[22]

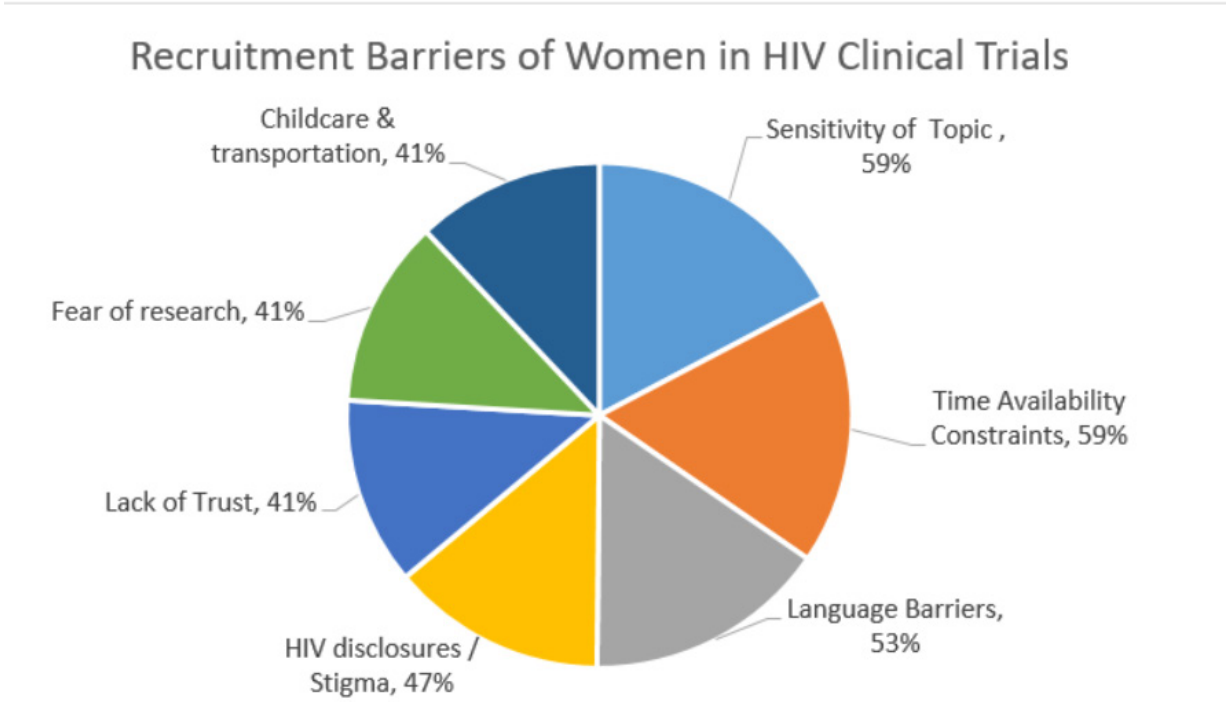
2.4 Barriers of Recruitment and Retention in Women

Many factors contributed to the absence of women participants in clinical trials, such as safety of the trials, voluntary withdrawals, distrust of the medical establishment, stigma, lack of community support, lack of childcare, lack of information about the study, and lack of transportation. These factors often played a vital role and affected the willingness of women to participate in research trials.[23] In a study conducted by Loufty et al. (2014), a survey was sent out to 38 site coordinators around Ontario, Canada, who were able to recruit 490 HIV positive women. The survey consisted of questions regarding study recruitment barriers. 34 out of 38 surveys were returned. Of those returned, 31 respondents were women. Figure 2 shows recruitment barriers of women in HIV clinical trials: 59% for the sensitivity of research topic and

[22] Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. (1999, January 1). Recruitment and Retention of Women in Clinical Studies: Theoretical Perspectives and Methodological Considerations. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK236563/.

[23] 20, S. on M. (2019, August 29). Lessons from GRACE: A US Study Focused on Women Living with HIV. Retrieved from https://www.thewellproject.org/hiv-information/lessons-grace-us-study-focused-women-living-hiv.

time constraints, at 53% for language barriers, 47% HIV disclosure/ Stigma issues, and 41% for childcare, transportation, fear of research, and lack of trust.[24]



2.4 Figure 2: Recruitment Barriers of Women in HIV Clinical Trials

Clinical research investigators have been found to not perform or report any gender analysis results, and have been found to recruit inadequate numbers of women to support the kind of subgroup analysis that would be needed to resolve these gender-specific questions.[25] Although current policies requiring the inclusion of women in clinical studies are in place, recruitment and retention of women in HIV clinical trials remain low. There is still inadequate

[24] Loutfy, M. R., V, L. K., Mohammed, S., Wu, W., Muchenje, M., Masinde, K., … Tharao, W. (2014, December 19). Recruitment of HIV-Positive Women in Research: Discussing Barriers, Facilitators, and Research Personnel's Knowledge. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4302460/.
[25] Mastroianni, A. C., Faden, R. R., & Federman, D. D. (1994). Women and health research ethical and legal issues of including women in clinical studies. Washington, D.C.: National Academy Press.

research data available for clinical trials with women participation, and many unanswered questions about gender-based differences in response to treatments remain.

2.5 Study Purpose

Based on the review of literature, women recruitment and retention rates in clinical trials remain low. An increase in recruitment and retention of female participants is needed to increase the validity of the clinical trial findings. Without the recruitment and retention of women in clinical trials, gender differences in response to medical treatment will remain unknown. This study will identify the common barriers of recruitment and retention of women in HIV/AIDS clinical trials and will identify the best practices to recruit and retain female participants in clinical trials.

2.6 Why is This Study Important?

Increasing the recruitment and retention of women in clinical trials is important to increase the validity of clinical trials and to transfer knowledge to all persons, both male and female.

Chapter 3

Problem Statement

Many past human immunodeficiency virus (HIV) clinical trials have struggled to recruit and retain female participants due to their encounters with potential barriers that prevented the participants' initial or continued participation in the clinical trials. Multiple studies found common barriers, such as distrust, language, childcare, transportation, and stigma. HIV/AIDS

still affects many women in the US, and there is a need to recruit and retain participants in HIV/AIDS clinical trials.[26] Studies have found that patients that withdrew early from clinical trials were unable to complete their treatment, resulting in disease progression.[27,28] A high rate of participation in clinical trials is crucial to the success of treatment programs in the total population of infected persons of both sexes. This study will focus on reviewing available data and identifying the best practices to overcome the common barriers of women recruitment and retention in HIV/AIDS clinical trials.

Chapter 4

Methodology

In order to find relevant data related to women's participation in HIV/AIDS clinical trials, keywords and terms were used in PubMed, BASE (Bielefeld Academic Search Engine), and Web of Science search portals. Although there are many additional search engines/portals available, these options were used for this study due to their extensive database of clinical and biomedical literature. Examples of search terms included a) *HIV/AIDS clinical trial with women*; b) *recruitment and retention of women in HIV/AIDS clinical trials*; c) Women *HIV recruitment AND retention barriers; and* d) *Successful strategies for recruitment of women participants in*

[26] Falcon, R., Bridge, D. A., Currier, J., Squires, K., Hagins, D., Schaible, D., … GRACE Study Group. (2011, July). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3130514/.

[27] Grewe, M. E., Ma, Y., Gilbertson, A., Rennie, S., & Tucker, J. D. (2016). Women in HIV cure research: multilevel interventions to improve sex equity in recruitment. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780361/.

[28] Krubiner, C. B., Faden, R. R., Cadigan, R. J., Gilbert, S. Z., Henry, L. M., Little, M. O., … Lyerly, A. D. (2016, September 24). Advancing HIV research with pregnant women: navigating challenges and opportunities. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014683/.

clinical trials. This study included articles related to the participation of women, the recruitment and retention of women subjects, the retention strategies and factors related to withdrawals of female participants, and the successful implementation of common best practices to improve women's participation in HIV/AIDS clinical studies.

The articles were further examined using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. PRISMA is used for the reporting of reviews and evaluations of randomized clinical trials and helps authors report a wide range of systematic reviews and meta-analyses that assess studies relating to healthcare intervention.[29] The PRISMA 2009 checklist includes 27 checklist items that focus on study details such as objectives, selection criteria, data collection processes, summaries of evidence, risks of bias across studies, limitations, and overall conclusions. These checklist items were used to help identify articles that described common barriers to recruitment and retention of women in HIV/AIDS clinical trials, and to identify the common best practices to minimize under-enrollment and participant withdrawals from clinical studies. Table 1, shown below, includes all the PRISMA criteria factors that were used for the selection process. Eighteen of these checklist items were used as the selection criteria for this study.

Topics/Section	Checklist items	Used for Selection Criteria	Not used for Selection Criteria
Title	Identify the report as a systematic review, meta-analysis, or both.	X	
Abstract	Provide a structured summary	X	

[29] (n.d.). Retrieved from http://www.prisma-statement.org/PRISMAStatement/HistoryAndDevelopment

Introduction	Describe the logic for the review in the context of what is already known	X	
Objectives	Provide an explicit statement of questions being addressed with reference to participants	X	
Methods	Indicate if a review protocol exists		X
Eligibility criteria	Specify study characteristics used as criteria for eligibility, giving rationale.	X	
Information Source	Describe all information sources	X	
Search	Present full electronic search strategy for at least one database	X	
Study Selection	State the process for selecting studies	X	
Date Collection	Describe the method of data extraction from reports	X	
Data items	List and define all variables (e.g. PICO, funding source)		X
Risk and bias	Describe methods used for assessing risk of bias during study or outcome level		X
Summary measure	State the principal summary measures (difference in means)		X
Synthesis of results	Describe the methods of handling data and combining results of studies	X	
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence	X	

Additional analyses	Describe methods of additional analyses (subgroup analyses, meta-regression)		X
Results	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage,	X	
Study characteristics	For each study, present characteristics for which data were extracted with citations	X	
Risk of bias within studies	Present data on risk of bias of each study		X
Results of individual studies	For all outcomes considered	X	
Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency		X
Risk of bias across studies	Present results of any assessment of risk of bias	X	
Additional analysis	Give results of additional analyses, if done		X
Discussion	Summarize the main findings including the strength of evidence for each main outcome	X	
Limitation	Discuss limitations at study and outcome level	X	
Conclusion	Provide a general interpretation of the results in the context of other evidence, and implications for future research	X	
Funding	Describe source of funding		X
Total	**27 checklist items**	**18 items included**	**9 items not included**

4.1 Table 1: PRISMA 2009 Checklist

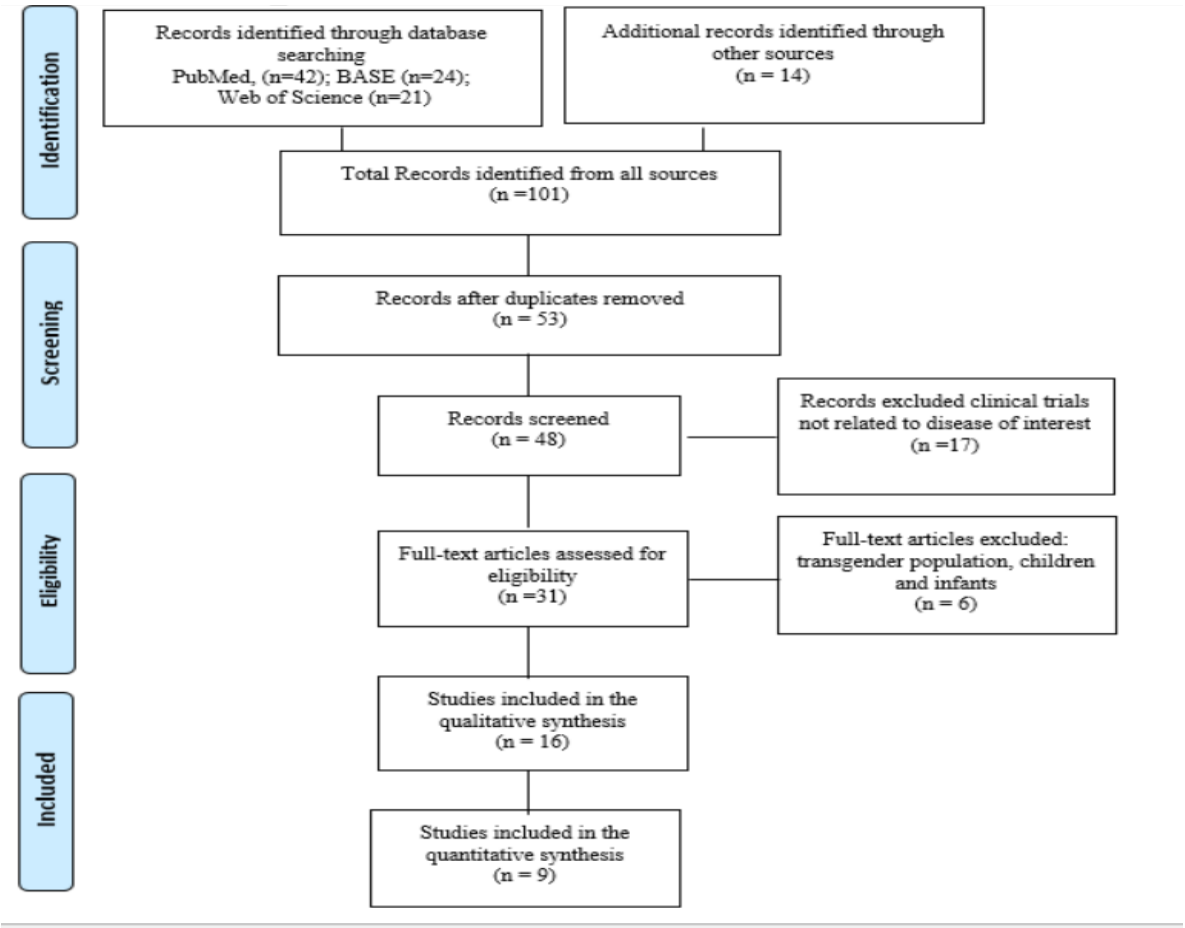
Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

doi:10.1371/journal.pmed1000097

A total of 101 records were identified using key terms in PubMed, BASE, and Web of Science search portals and were put into an Excel spreadsheet. Articles were then sorted by author, title, and year. Fifty-three results were found to be duplicates and were removed. The 48 remaining records were then screened using the articles' abstracts. After this review, 17 articles contained clinical data that were unrelated to the disease of interest and were excluded. The remaining 31 full-text articles were assessed for eligibility. These were further analyzed by looking at the articles' data results, and six were excluded due to the inclusion of transgender men/women, children, and infants. Twenty-five full-text articles remained and were thoroughly examined.

Using the PRISMA checklist for selection criteria, articles were then sorted into two categories: qualitative and quantitative articles. Of these studies, 16 were categorized into qualitative synthesis, which involved one-on-one interactions between staff and participants, and healthcare providers' observations. The remaining nine studies were categorized into quantitative synthesis, which included surveys and questionnaires provided by the researchers.

Comparative analysis of the 25 articles identified common practices used for recruiting female participants in HIV/AIDS clinical trials. Each article was reviewed using the same method: by examining the common barriers and common best practices in recruiting and retaining women participants. Figure 3, shown below, was used to give a graphical representation of the selection process for relevant studies.



4.2 Figure 3: PRISMA 2009 Flow Diagram Flow diagram for the systematic review of qualitative and quantitative studies regarding recruitment barriers and successful strategies of women in HIV/AIDS clinical trials. Source: Moher, et al[30]

Chapter 5

Data Analysis

The 25 studies showed eight common recruitment and retention barriers. These barriers were identified through observation by the study subjects' healthcare providers or a follow-up survey that was given by the research staff.

[30]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

There were 16 (64%) qualitative articles and 9 (36%) quantitative articles. Of the qualitative articles; 75% (n=12) of the articles recorded data during a one-on-one interaction between healthcare staff and participants, 62.5% (n=10) of the articles used observations from healthcare providers to record data relating to recruitment and retention rates of women in clinical trials, and 25% (n=4) of the articles mentioned the impact of community social groups on enrollment in clinical trials. Of the quantitative articles, 33.3% (n=3) of the articles recorded data using surveys provided to participants by clinical staff, and 66.6% (n=6) of the articles used questionnaires to record data, shown below in Table 2.

Article Type	**Total Articles No. (%)**	**One on One interaction between patients and Healthcare Staff No. (%)**	**Observation from healthcare providers No. (%)**	**Impact of Social groups No. (%)**
Qualitative	16 (64.0)	12 (75.0)	10 (62.5)	4 (25.0)
Article Type	**Total Article No. (%)**	**Surveys No. (%)**	**Questionnaires No. (%)**	
Quantitative	9 (36.0)	3 (33.3)	6 (66.6)	
Total	**25**			

5.1 Table 2: Distribution of Reviewed Articles by both Qualitative and Quantitative Methods of Recruitment of Women participants in HIV/AIDS Clinical Trials

The research findings identified common barriers in recruitment and retention in HIV clinical trials for women. The four most common barriers reported among the female HIV/AIDS population were negative social stigma, lack of trust, difficulty finding childcare, and lack of

transportation.[31] Other common barriers included language barriers, sensitivity to the study topic, safety of the treatment, inadequate research knowledge, and fear of research.[32]

Social stigma was reported as the most common barrier and was seen in 34.6% (n=9) of all reviewed articles in this study; lack of trust was reported as the second most common barrier and appeared in 24.0% (n=6); childcare and transportation together were reported as the third most common barrier and were seen in 20% (n=5), as shown in Table 3.

Barriers	**Articles No (%)**	**Barriers Examples**	**Best Practices**
Social Stigma	9 (34.6)	Female less likely to engage independently in research, negative experience	The rapport between Personnel and Participants, empathetic
Lack of Trust	6 (24.0)	A misconception or misinformation surrounding research	Building trust between study personnel and participant
Childcare and Transportation	5 (20.0)	Limited access	Location of sites needed to be closer to participants, flexibility
Language Barriers	4 (16.0)	Low level of language proficiency	Personnel and participants from similar cultures
Sensitivity to topic	3 (12.0)	Personal topics of sexual and reproductive health	Acknowledgment of sensitive topics
Safety of Treatment	3 (12.0)	Community engagement	Skilled and knowledgeable about the research
Inadequate Research knowledge	3 (12.0)	Limited evidence of successful trials	Staff Training and patient follow-up

[31] George, S., Duran, N., & Norris, K. (2014). A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. American journal of public health, 104(2), e16–e31. https://doi.org/10.2105/AJPH.2013.301706

[32] Krubiner, C. B., Faden, R. R., Cadigan, R. J., Gilbert, S. Z., Henry, L. M., Little, M. O., Mastroianni, A. C., Namey, E. E., Sullivan, K. A., & Lyerly, A. D. (2016). Advancing HIV research with pregnant women: navigating challenges and opportunities. *AIDS (London, England)*, *30*(15), 2261–2265. https://doi.org/10.1097/QAD.0000000000001214

Fear of Research	2 (8.0)	Discussing or revisiting sensitive topics	Debriefing after completion of a questionnaire

5.2 Table 3: Data Results of Common Barriers of Recruitment and Retention of Women Participants in HIV/AIDS Clinical Trials with Common Best Practices
*Total number of reviewed article 25

As a result of the observations and surveys, several common best practices were found to increase women's participation and retention in clinical HIV/AIDS studies. Researchers found that having a support group and a research staff member of a similar cultural background to facilitate the study helped with recruitment and retention of female participants. Having a supportive relationship between the study subject and research staff was also essential to maintain high retention rates in clinical trials.

Chapter 6

Discussion of Data Results

Healthcare providers and researchers were able to identify and implement several common best practices to address these barriers. Participants were less likely to engage independently in research studies due to negative experiences relating to social stigma. In addressing negative social stigma, researchers found the best practice was to build a relationship between personnel and participants. Researchers wanted to remain transparent by giving the participants the opportunity to ask questions or voice their concerns to clarify any misconceptions or misinformation surrounding the research study. Researchers were able to provide more convenient study sites and appointment times to accommodate the participants' lack of transportation and difficulties finding childcare. Healthcare providers observed that some participants had low levels of English language proficiency, and in response, hired

personnel with similar language and cultural backgrounds to assist with the language barrier. Clinical research staff acknowledged sensitive topics relating to HIV/AIDS and gave participants the opportunity to ask questions. Research coordinators who specialized in HIV clinical studies were hired to help participants who had inadequate knowledge about the research topic, or who were concerned about the safety of the trials. The clinical staff gave participants debriefings after the completion of clinical visits to address the participants' fears and concerns relating to the studies.

Several recommendations can be made to implement these best practices to address the common barriers that resulted in the low recruitment and retention rates of female participants in future HIV/AIDS clinical studies. These recommendations include providing participants with monetary incentives, handing out brochures or fliers with research study information, using social media to spread awareness of the studies, offering online scheduling for appointments and follow-ups, offering video chat appointments, having an after-hour consultation service for questions or concerns, teaming with a local community center for support, hiring multilingual research staff or translators, providing online forms for surveys and questionnaires, and having in-house visits for participants unable to find childcare or transportation.

6.1 Limitations

There were several limitations in this study that may have impacted data analysis. While the initial literature search yielded a large number of existing articles, only 25 full-text articles relating to women's participation in HIV/AIDS clinical trials were available for analysis for this study. The reference data did not come only from participants; it also included research

personnel and healthcare providers' perspectives. These perspectives could have been substituted for the participants' actual clinical experience. Each HIV/AIDS clinical trial had a set of specific eligibility criteria, requirements, and inherent biases. Furthermore, what was successful for one study group may not have been successful for the other groups.

Chapter 7

Conclusion

Based on the data found in this study, there were several common barriers to the recruitment and retention of female subjects in HIV/AIDS clinical trials. These barriers needed to be addressed to maximize the number of participants enrolled and to minimize the number of participant withdrawals. By acknowledging the common barriers and implementing the best practices found in this study, healthcare providers and researchers will be able to overcome the challenges in recruiting and retaining female participants in HIV/AIDS clinical trials. These common best practices, such as building relationships between patients and providers, acknowledging sensitive topics, training staff to be more knowledgeable about HIV/AIDS, showing empathy toward participants, and providing scheduling and location flexibility for patients, are some of the ways to help researchers improve the recruitment and retention rates of study subjects.

Improving the recruitment and retention of women in HIV/AIDS clinical trials is essential to increase the validity of clinical trials and the knowledge for all persons, both male and female, due to gender-based differences in their responses to medical treatment. HIV/AIDS clinical trials are crucial to the success of treatment programs to minimize the burden of

HIV/AIDS on the total population of infected persons of both sexes. Additional research involving women subjects in HIV/AIDS clinical studies would be beneficial in improving clinical outcomes.

Bibliography

1. Loutfy, M. R., V, L. K., Mohammed, S., Wu, W., Muchenje, M., Masinde, K., Tharao, W. (2014, December 19). Recruitment of HIV-Positive Women in Research: Discussing Barriers, Facilitators, and Research Personnel's Knowledge. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4302460/.

2. Learn About Clinical Studies. (n.d.). Retrieved from https://clinicaltrials.gov/ct2/about-studies/learn#WhatIs
3. Why Should I Participate in a Clinical Trial? (2019, May 30). Retrieved from https://www.nih.gov/health-information/nih-clinical-research-trials-you/why-should-i-participate-clinical-trial

4. Fogel D. B. (2018). Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemporary clinical trials communications*, *11*, 156–164. https://doi.org/10.1016/j.conctc.2018.08.001

5. Hwang T.J., Carpenter D., Lauffenburger J.C., Wang B., Franklin J.M., Kesselheim A.S. Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA Intern. Med. 2016;176:1826–1833

6. Metch, B., Frank, I., Novak, R., Swann, E., Metzger, D., Morgan, C., . . . Koblin, B. (2013). Recruitment of urban
US women at risk for HIV infection and willingness to participate in future HIV vaccine trials. AIDS Behav, 17(2), 760-772. doi:10.1007/s10461

7. History of HIV Vaccine Research. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history

8. A Theoretical Approach To HIV Vaccine Development. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/theoretical-approach
9. An Empirical Approach to HIV Vaccine Development. (n.d.). Retrieved from https://www.niaid.nih.gov/diseases-conditions/empirical-approach

10. Inclusion of Women in Clinical Trials: A Historical Overview of Scientific Ethical and Legal IssuesMerkatz, Ruth B. Journal of Obstetric, Gynecologic & Neonatal Nursing, Volume 27, Issue 1, 78 – 84

11. Pearl et al., 1992Pearl, M., Banzhaf, M., Leger, A., and Long, I.L. Women in U.S. government clinical trials. Amsterdam, Netherlands; 1992 (VIII International Conference on AIDS, 8(2:B235))

12. Institute of Medicine (US) Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies; Mastroianni AC, Faden R, Federman D, editors. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies: Volume I. Washington (DC): National Academies Press (US); 1994. 2, Women's Participation in Clinical Studies. Available from: https://www.ncbi.nlm.nih.gov/books/NBK236535/

13. S. on M. (2019, August 29). Lessons from GRACE: A US Study Focused on Women Living with HIV. Retrieved from https://www.thewellproject.org/hiv-information/lessons-grace-us-study-focused-women-living-hiv.

14. Centers for Disease Control and Prevention. HIV/AIDS among women. www.cdc.gov/hiv/topics/women/resources /factsheets/pdf. [Jul 20;2010] www.cdc.gov/topics/women/resources/factsheets/pdf.

15. Falcon, R., Bridge, D. A., Currier, J., Squires, K., Hagins, D., Schaible, D., . . . Mrus, J. (2011). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. J Womens Health (Larchmt), 20(7), 1043-1050. doi:10.1089/jwh.2010.2504

16. Cargill, V. A., & Stone, V. E. (2005). HIV/AIDS: a minority health issue. *Med Clin North Am, 89*(4), 895-912. doi:10.1016/j.mcna.2005.03.005

17. Mastroianni, A. C., Faden, R. R., & Federman, D. D. (1994). Women and health research ethical and legal issues of including women in clinical studies. Washington, D.C.: National Academy Press.

18. Grewe, M. E., Ma, Y., Gilbertson, A., Rennie, S., & Tucker, J. D. (2016). Women in HIV cure research: multilevel interventions to improve sex equity in recruitment. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780361/.

19. Krubiner, C. B., Faden, R. R., Cadigan, R. J., Gilbert, S. Z., Henry, L. M., Little, M. O., Lyerly, A. D. (2016, September 24). Advancing HIV research with pregnant women: navigating challenges and opportunities. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014683/.

20. (n.d.). Retrieved from http://www.prismastatement.org/PRISMAStatement/HistoryAndDevelopment

21. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.doi:10.1371/journal.pmed1000097

22. George, S., Duran, N., & Norris, K. (2014). A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. American journal of public health, 104(2), e16–e31. https://doi.org/10.2105/AJPH.2013.301706

23. Krubiner, C. B., Faden, R. R., Cadigan, R. J., Gilbert, S. Z., Henry, L. M., Little, M. O., Mastroianni, A. C., Namey, E. E., Sullivan, K. A., & Lyerly, A. D. (2016). Advancing HIV research with pregnant women: navigating challenges and opportunities. AIDS (London, England), 30(15), 2261–2265. https://doi.org/10.1097/QAD.0000000000001214

Biographical Statement

Katie Ta was raised in a catholic home with her parents and seven siblings. She has always had an aspiration to become a research medical doctor. However, raising three kids of her own was not an easy task, so she decided to put her goals on pause. In 2010, she enrolled in a Community College. She transferred a year later to the University of Nebraska after receiving a full-ride scholarship from The Susan Thompson Buffett Foundation. Katie volunteered at the University of Nebraska Medical Center during her undergraduate years as a way to give back to the community. In May of 2014, she received her B.A in Biology. In 2015, Katie decided to move to Texas to be closer to her family and to pursue new opportunities. In the fall of 2017, she decided to enroll in the Johns Hopkins University Master of Science program to further her career in research. In the spring of 2020, she received her M.S in Research Administration. Katie is currently a Grant Specialist at Rice University, Houston, Texas.